IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al.

Application No.: 10/626,499 Art Unit 1625

Filed: July 24, 2003 Examiner: C. C. Chang

For: A PROCESS FOR PREPARATION OF DONEPEZIL

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal that was filed on March 6, 2006 for the subject application, a brief in support of the appeal is now submitted. Payment of the $500.00 fee specified by 37 C.F.R. § 41.20(b)(2) is being made with this submission.

As this submission is not being made within the prescribed period, a petition for extending the period to June 6, 2006 is also being submitted.

1. Real Party in Interest

The real parties in interest are Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., assignees of the application from the inventors/appellants.

2. Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

3. Status of the Claims

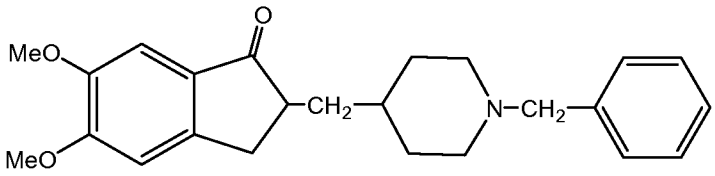
Claims 1-33 were finally rejected in an Office Action mailed on November 9, 2005 and are the subject of this appeal.

4. Status of Amendments

No amendment has been filed subsequent to final rejection.

5. Summary of Claimed Subject Matter

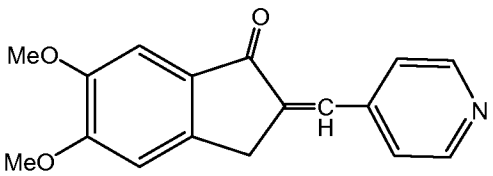
The claimed subject matter encompasses a process for preparing the drug compound donepezil, which, in the form of a hydrochloride salt, is the active component in pharmaceutical products sold for the treatment of Alzheimer's Disease. Donepezil has the following structural formula (I).



(I)

Independent claim 1 is directed to a process for preparation of donepezil, the process comprising the steps of:

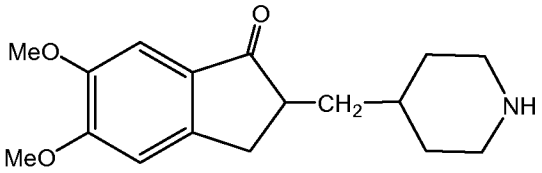
a) suspending a compound of the formula (IV):



(IV)

and a catalyst, which is palladium metal on a support carrier, in an alcoholic solvent; [US 2004/013121 A1, page 1, ¶¶ 0008-0009]

b) hydrogenating the suspension at the hydrogen pressure of from about 1 to about 5 atmospheres and a temperature of from about 40 to about 90° C. until the hydrogenation reaction is substantially complete to obtain a compound of the formula (VI):



(VI) ;

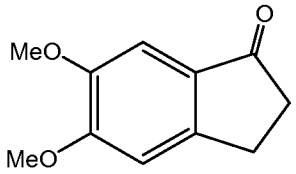
[US 2004/013121 A1, page 1, ¶ 0010]

c) isolating said compound of formula (VI); [US 2004/013121, page 1, ¶ 0011] and

d) converting said compound of the formula (VI) to donepezil. [US 2004/013121, page 1, ¶ 0012]

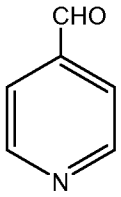
Independent claim 19 is directed to a process for preparation of donepezil, this process comprising the steps of:

a. refluxing a mixture of 5,6-dimethoxy indanone of the formula (II)



(II)

and pyridine-4-carboxaldehyde of the formula (III)



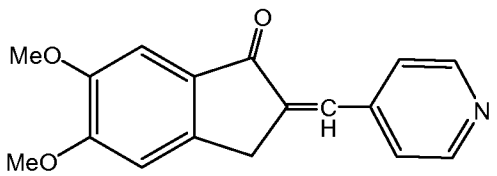
(III)

in toluene in the presence of p-toluene sulfonic acid until the reaction is substantially complete thereby a solid is formed; [US 2004/013121, page 2, ¶ 0016]

b. cooling the reaction mixture to ambient temperature and filtering the solid; [US 2004/013121 A1, page 2, ¶ 0017]

c. suspending the filtered solid in an aqueous basic solution and stirring the suspension; [US 2004/013121 A1, page 2, ¶ 0018]

d. filtering the solid obtained in step c. to afford 5,6 dimethoxy-2(pyridin-4-yl)-methylene indan-1-one of the formula (IV):



(IV) ;

[US 2004/013121 A1, page 2, ¶ 0019]

e. suspending the compound of the formula (IV) and palladium on carbon in an alcoholic solvent selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol and tertiary butanol in the presence of acetic acid in a hydrogenation vessel; [US 2004/013121 A1, page 2, ¶ 0020]

f. heating the reaction mixture of step e. under 1-5 atmospheres hydrogen pressure at a temperature of 40 to 90° C. until the reaction substantially completes; [US 2004/013121 A1, page 2, ¶ 0021]

g. cooling of the reaction mass of step f. to ambient temperature followed by filtering the catalyst; [US 2004/013121 A1, page 2, ¶ 0022]

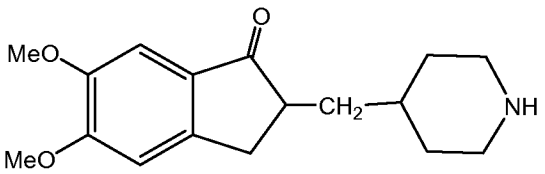
h. distilling the solvent from the filtrate obtained in step g. to get a residue; [US 2004/013121 A1, page 2, ¶ 0023]

i. dissolving the residue obtained in step h. in water and followed by washing with a chloro solvent selected from the group consisting of dichloromethane, dichloroethane, chloroform and carbon tetrachloride, and separating the aqueous layer; [US 2004/013121 A1, page 2, ¶ 0024]

j. adjusting the pH of the aqueous layer of step i. to 9 to 14 with a base solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; [US 2004/013121 A1, page 2, ¶ 0025]

k. extracting the compound from the basified aqueous layer of step j. with an organic solvent selected from the group consisting of dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether and petroleum ether; [US 2004/013121 A1, page 2, ¶ 0026]

l. distilling the solvent from the reaction solution of step k., followed by triturating the residue in a non-polar organic solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, cyclo heptane, di ethyl ether, di isopropyl ether, di isobutyl ether and methyl tertiary butylether and petroleum ether, to afford 5,6-dimethoxy-2-piperidin-4-yl methyl-indan-1-one of the formula (VI):



(VI) ;

[US 2004/013121 A1, page 3, ¶ 0027]

m. reacting the compound of the formula (VI) with benzyl bromide in a solvent selected from the group consisting of methanol, ethanol isopropanol, butanol acetone, ethylmethyl ketone, and 2-butanone in the presence of a base selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethyl amine, tributyl amine, tertiary butyl amine and pyridine at a temperature of 30-80°C., until the reaction substantially completes; [US 2004/013121 A1, page 3, ¶ 0028]

n. cooling the reaction mass to ambient temperature and followed by filtering the mass; [US 2004/013121 A1, page 3, ¶ 0029]

o. diluting the filtrate obtained in step n. with water and further extracting the compound into ether solvents selected from the group consisting of isopropyl ether, methy tertiary butylether, diethyl ether, toluene, benzene, ethyl benzene, xylene, hexane, cyclohexane and petroleum ether; [US 2004/013121 A1, page 3, ¶ 0030]

and

p. distilling the solvent from the reaction solution of step o. followed by triturating the residue in a non-polar organic solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, cyclo heptane, di ethyl ether, di isopropyl ether, di isobutyl ether, methyl tertiary butylether and petroleum ether, to obtain donepezil. [US 2004/013121 A1, page 3, ¶ 0031]

The dependent claims are directed to various embodiments of the disclosed donepezil preparation process.

A copy of the appealed claims is appended hereto, in an appendix beginning on page 17.

6. Grounds of Rejection to be Reviewed on Appeal

A. Whether claims 1, 2, 4-6 and 8-12 are unpatentable under 35 U.S.C. § 102(e) as anticipated by U.S. Patent 6,649,765 to Vidyadhar et al. (hereinafter "Vidyadhar").

B. Whether claims 1, 2, 4-6 and 8-12 are unpatentable under 35 U.S.C. § 103(a) as obvious over Vidyadhar in view of U.S. Patent No. 4,895,481 to Sugimoto et al. (hereinafter "Sugimoto I").

C. Whether claims 1, 2, 4-6 and 8-12 are unpatentable under 35 U.S.C. § 103(a) as obvious over Vidyadhar in view of Sugimoto I and Sugimoto et al., *Bioorog. Med. Chem. Let.* 2:871-876 (1992) (hereinafter "Sugimoto II), and further in view of WO 97/22584 to Devries (hereinafter "Devries").

D. Whether claims 1, 2, 4-6, 8, 9, 11 and 12 are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,606,864 to Lensky (hereinafter "Lensky") in view of Sugimoto I.

E. Whether claims 1, 2, 4-6, 8, 9, 11 and 12 are unpatentable under 35 U.S.C. § 103(a) as obvious over Lensky in view of Sugimoto I and Sugimoto II.

F. Whether claims 1-33 are unpatentable under 35 U.S.C. § 103(a) as obvious over Lensky in view of Sugimoto I and Sugimoto II and further in view of Devries.

7. Argument

A. Rejection Under 35 U.S.C. § 102(e)

Claims 1, 2, 4-6 and 8-12 stand finally rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Vidyadhar. In the Office Action mailed March 2, 2005, the Examiner contends that Vidyadhar discloses all the elements of claim 1 (as well as

dependent claims 2, 4-6 and 8-12) in very explicit description, citing to Examples 1 and 2. Regarding the hydrogenation catalyst, the Examiner states that platinum or palladium oxide are disclosed, with only platinum oxide exemplified.

To fulfill the requirements for a priority claim under 35 U.S.C. § 119, Appellants submitted a certified copy of India Patent Application 555/MAS/2002 on August 24, 2005. This Indian priority document was filed on July 24, 2002, well before the § 102(e) date for Vidyadhar, that date being February 12, 2003.

The Examiner, however, failed to accept Appellants' priority claim. In the Office Action mailed November 9, 2005 and the Advisory Action mailed February 2, 2006, the Examiner contends that the priority document discloses a sixteen step process, while claim 1 of the instant application discloses a four step process, thus making them "different inventions" not entitled to priority. Thus, according to the Examiner, the rejection over Vidyadhar is proper.

Regarding a claim of priority under § 119, MPEP § 2163.03 states in relevant part:

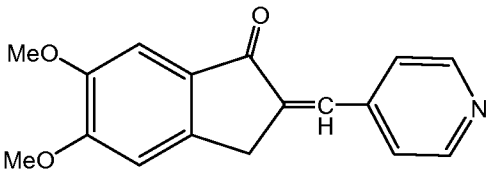
> Under 35 U.S.C. 119 (a) or (e), the claims in a U.S. application are entitled to the benefit of a foreign priority date or the filing date of a provisional application if the corresponding foreign application or provisional application supports the claims in the manner required by 35 U.S.C 112, first paragraph. *In re Ziegler*, 992 F.2d 1197, 1200, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993); *Kawai v. Metlesics*, 480 F.2d 880, 178 USPQ 158 (CCPA 1973); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Thus, claim 1 of the instant application is entitled to a claim of priority to India Patent Application 555/MAS/2002 if there is written support for the claim under § 112. Regarding written description, MPEP § 2163.02 states in relevant part:

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams,

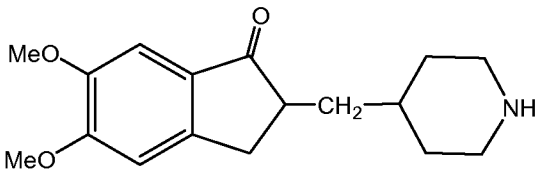
> and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.

In the instant case, India Patent Application 555/MAS/2002 clearly shows that Appellants were in possession of the process for preparing donepezil recited in claim 1. In particular, the process set forth on pages 6-9 of the priority document describes each and every limitation of the process recited in claim 1 of the instant application. First, step e) at page 7 of the priority document describes suspending a compound of the formula (IV):



(IV)

and palladium on carbon in an alcoholic solvent. Next, step f) at page 7 of the priority document describes hydrogenating the suspension at 1 to 5 atmospheric hydrogen pressures and a temperature of from 40 to 90° C. until the hydrogenation reaction is substantially complete to obtain a compound of the formula (VI):



(VI)

Next, steps g) to l) at pages 7-8 of the priority document describe isolating the compound of formula (VI). Finally, steps m) to p) at pages 8-9 of the priority document describe converting the compound of formula (VI) to donepezil.

The fact that the process set forth in the priority document has more steps than claim 1 of the instant application is of no moment. First, claim 1 is a "comprising" claim, allowing for the performance of additional steps. Second, the additional steps recited in the priority document are directed to a) providing the compound of formula (IV); b) isolating the compound of formula (VI); and c) converting the compound of formula (VI) to donepezil. Nothing in the priority document indicates that these additional steps are essential elements of the disclosed process. In fact, the Summary of the Invention at page 5 of the priority document specifically states:

> More particularly the improved process of the present invention comprises preparation of key intermediate of formula (VI) by palladium-catalyzed hydrogenation of compound Formula (IV), followed by conversion to Donepezil.

Thus, the priority document makes clear that the invention disclosed therein comprises the same steps now recited in claim 1 of the instant application. As such, Vidyadhar is not prior art to claim 1, and thus cannot anticipate the claimed subject matter.

Similarly, Vidyadhar is not prior art to claims 2, 4-6 and 8-12 of the instant application. Claim 2 depends from claim 1 and further comprises specific steps for isolating the compound of formula (VI), each of which are described in steps g) to l) at pages 7-8 of the priority document. Claims 4-6 depend from claim 1 and recite specific hydrogenation conditions, each of which are described in step e) at page 7 of the priority document. Claims 8-9 depend from claim 2 and specify specific isolation conditions, each of which are described in steps j) to k) at pages 7-8 of the priority

document. Claim 10-12 depend from claim 1 and specify specific conversion conditions, each of which are described in step m) at page 8 of the priority document.[1] Thus, as with claim 1, Vidyadhar is not prior art to claims 2, 4-6 and 8-12 of the instant application, and thus cannot anticipate the claimed subject matter.

Furthermore, even if Vidyadhar were properly citable as prior art, it has long been the law that anticipation can properly be held only where a prior art document teaches each and every limitation of the rejected claim. *See Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 2 USPQ2d 1051 (Fed. Cir. 1987). Here, each of the rejected claims are directed to a process for preparing donepezil comprising the step of hydrogenating 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one using a palladium metal on a support carrier. In contrast, as the Examiner acknowledges, Vidyadher teaches a process for preparing donepezil hydrochloride comprising the step of hydrogenating 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one with a noble metal oxide catalyst. Nowhere does Vidyadher teach, or even suggest, the use of palladium metal on a support carrier to hydrogenate 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one.

Accordingly, Appellants submit that no case for anticipation of claims 1, 2, 4-6 and 8-12 has been made out, and the rejection should not be sustained.

B. First Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6 and 8-12 stand finally rejected under 35 U.S.C. § 103(a) as allegedly obvious over Vidyadhar in view of Sugimoto I. According to the Examiner in the Office Action mailed March 2, 2005, Sugimoto I discloses processes for making compounds analogous to the compound of formula (I), as well as the compound of formula (I), using a catalyst composed of palladium-carbon. Thus, according to the

[1] In claim 8, the extractants are incorrectly listed as "selected from the group consisting of dichloromethane, dichloroethane, chloroform and carbon tetrachloride." The extractants should be listed as "selected from the group consisting of dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether and petroleum ether." *See* US 2004/013121 A1, p. 2, ¶ 0026. In claim 10, the phrase "wherein said step of converting the compound of formula (IV) to the compound of formula (I)" should recite "wherein said step of converting the compound of formula (VI) to the compound of formula (I)." *See* US 2004/013121 A1, p. 3, ¶ 0028. These inadvertent errors do not affect the issues on appeal and will be corrected upon indication that the claims are allowable.

Examiner, one of ordinary skill in the art would be motivated to choose the palladium-carbon catalyst of Sugimoto I to carry out the reaction of Vidyadhar because it is well known that platinum oxide is costly.

As discussed above, Vidyadhar is not properly citable as prior art because Appellants are entitled to the filing date of their priority document under 35 U.S.C. § 119. As such, the combination of Vidyadhar and Sugimoto I cannot render obvious claims 1, 2, 4-6 and 8-12.

Furthermore, even if Vidyadhar were properly citable as prior art, the combination of Vidyadhar and Sugimoto I would not render obvious claims 1, 2, 4-6 and 8-12. The standards for making an obviousness rejection are summarized in MPEP § 706.02(j), as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Thus, to sustain the rejection of obviousness, the prior art references must provide all the limitations of claims 1, 2, 4-6 and 8-12. As discussed above, Vidyadhar teaches a process for preparing donepezil hydrochloride comprising the step of hydrogenating 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one with a noble metal oxide catalyst. Sugimoto I, on the other hand, describes a process for preparing donepezil involving hydrogenation of 1-benzyl-4[5,6-dimethoxy-1-indanon)-2-ylidenyl]-methylpiperidine using palladium carbon in a THF solution. (*See* col. 34, Example 4.) Neither of the cited references teaches or suggests hydrogenation of 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one (compound of formula (IV)), let alone with palladium metal on a support carrier. As such, the combination of Vidyadhar and

Sugimoto I fails to provide each and every limitation of claims 1, 2, 4-6 and 8-12 as is required for a finding of obviousness.

Accordingly, Appellants submit that no case of obviousness for claims 1, 2, 4-6 and 8-12 has been made out, and the rejection should not be sustained.

C. Second Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6 and 8-12 stand finally rejected under 35 U.S.C. § 103(a) as allegedly obvious over Vidyadhar in view of Sugimoto I and Sugimoto II in further view of Devries. According to the Examiner in the Office Action mailed March 2, 2005, Sugimoto II supplies the factual evidence of the general teaching of Sugimoto I regarding palladium carbon, while Devries discloses analogous processes for making the compound of formula (I). Thus, according to the Examiner, one of ordinary skill in the art would be motivated to choose the palladium-carbon catalyst of Sugimoto I and II to carry out the reaction of Vidyadhar because it is well known that platinum oxide is costly. Further, according to the Examiner, the limitations in the dependent claims are alternative operating parameters suggested in Devries.

As discussed above, Vidyadhar is not properly citable as prior art because Appellants are entitled to the filing date of their priority document under 35 U.S.C. § 119. As such, the combination of Vidyadhar, Sugimoto I, Sugimoto II and Devries cannot render obvious claims 1, 2, 4-6 and 8-12.

Furthermore, even if Vidyadhar, were properly citable as prior art, the combination of Vidyadhar, Sugimoto I, Sugimoto II and Devries would not render obvious claims 1, 2, 4-6 and 8-12.

As discussed above, to sustain the rejection of obviousness, the prior art references must provide all the limitations of claims 1, 2, 4-6 and 8-12. Vidyadhar and Sugimoto I are described above. Sugimoto II describes a general synthetic route for the synthesis of a class of compounds, one of which is donepezil, which is very similar to the synthesis of donepezil described in Sugimoto I. (*See* page 872, Scheme 1.) That is, Sugimoto II teaches to one of ordinary skill in the art the hydrogenation of 1-benzyl-4[5,6-dimethoxy-1-indanon)-2-ylidenyl]-methylpiperidine using palladium carbon, and, as such, adds nothing over Sugimoto I. Devries discloses a scheme for the preparation

of donepezil, but the starting material is 4-(5,6-dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester, not 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one. (*See* page 9, Scheme 2; pages 17-18, Examples 4-6.) As such, no hydrogenation is disclosed. None of the cited references teaches or suggests hydrogenation of 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one (compound of formula (IV)), let alone with palladium metal on a support carrier. As such, the combination of Vidyadhar, Sugimoto I, Sugimoto II and Devries fails to provide each and every limitation of claims 1, 2, 4-6 and 8-12 as is required for a finding of obviousness.

Accordingly, Appellants submit that no case of obviousness for claims 1, 2, 4-6 and 8-12 has been made out, and the rejection should not be sustained.

D. Third Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6 and 8, 9, 11 and 12 stand finally rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lensky in view of Sugimoto I. According to the Examiner in the Office Action mailed March 2, 2005, Lensky discloses similar steps for a process, albeit in a different order, for making the compound of formula (I) using exemplified platinum dioxide or generic palladium on carbon. Thus, according to the Examiner, one of ordinary skill in the art would have found choosing the alternative palladium carbon catalyst of Sugimoto I *prima facie* obvious. Further, according to the Examiner, the changing of the sequence of alkylation and hydrogenation would also have been prima facie obvious because such derivatization steps are independent for different functional groups.

As discussed above, to sustain the rejection of obviousness, the prior art references must provide all the limitations of claims 1, 2, 4-6 and 8, 9, 11 and 12. Sugimoto I is described above. Lensky describes a process for the preparation of donepezil involving alkylation of 5,6-dimethoxy-2-(pyridine-4-yl)-methylene-indan-1-one to 1-benzyl-4-(5,6-dimethoxyindan-1-on-2-ylidene)-methyl-pyridinium bromide, followed by hydrogenation to donepezil using platinum dioxide, with an overall yield of 58.5%. The hydrogenation of 1-benzyl-4-(5,6-dimethoxyindan-1-on-2-ylidene)-methyl-pyridinium bromide in Lensky is very similar to the hydrogenation of 1-benzyl-4[5,6-dimethoxy-1-indanon)-2-ylidenyl]-methylpiperidine in Sugimoto I. As such, although the

process in Lensky begins with 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one (compound of formula (IV)), there is no teaching or suggestion of its hydrogenation as recited in the instant claims, let alone with palladium metal on a support carrier. Thus, there is also no teaching or suggestion of the conversion of 5,6-Dimethoxy-2-piperidin-4-yl methyl-indan-1-one (compound of formula (VI)) to donepezil, as also recited in the instant claims. The Examiner's contention that the changing of the sequence for alkylation and hydrogenation found in Lensky is *prima facie* obvious is belied by the fact that the relevant steps of Appellants' process yield donepezil at an overall rate of 88% (*see* Appellants' Examples 2 and 3), while the relevant steps of Lensky's process yield donepezil at an overall rate of only 67% (*see* pages 4-5, Examples 4 and 6).

Accordingly, Appellants submit that no case of obviousness for claims 1, 2, 4-6, 8, 9, 11 and 12 has been made out, and the rejection should not be sustained.

E. Fourth Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6 and 8, 9, 11 and 12 stand finally rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lensky in view of Sugimoto I and Sugimoto II. According to the Examiner in the Office Action mailed March 2, 2005, Sugimoto II supplies the factual evidence of the general teaching of Sugimoto I regarding palladium carbon. Thus, according to the Examiner, one of ordinary skill in the art would have found choosing the alternative palladium carbon catalyst of Sugimoto I and Sugimoto II *prima facie* obvious. Further, according to the Examiner, the changing of the sequence of alkylation and hydrogenation in Lensky would also have been prima facie obvious because such derivatization steps are independent for different functional groups.

The discussion above regarding the third obviousness rejection fully applies to this rejection. Lensky discloses hydrogenation of 1-benzyl-4-(5,6-dimethoxyindan-1-on-2-ylidene)-methyl-pyridinium bromide using platinum dioxide. Sugimoto I and Sugimoto II teach hydrogenation of 1-benzyl-4[5,6-dimethoxy-1-indanon)-2-ylidenyl]-methylpiperidine using palladium carbon. None of the cited references teaches or suggests hydrogenation of 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one (compound of formula (IV)), let alone with palladium metal on a support carrier. As such, the combination of Vidyadhar, Sugimoto I and Sugimoto II fails to provide each

and every limitation of claims 1, 2, 4-6 and 8, 9, 11 and 12 as is required for a finding of obviousness.

Accordingly, Appellants submit that no case of obviousness for claims 1, 2, 4-6, 8, 9, 11 and 12 has been made out, and the rejection should not be sustained.

F. Fifth Rejection Under 35 U.S.C. § 103(a)

Claims 1-33 stand finally rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lensky in view of Sugimoto I and Sugimoto II and further in view of Devries. According to the Examiner in the Office Action mailed March 2, 2005, Devries discloses analogous processes for making the compound of formula (I). Thus, according to the Examiner, one of ordinary skill in the art would have found choosing the alternative palladium carbon catalyst of Sugimoto I and Sugimoto II *prima facie* obvious. Further, according to the Examiner, the changing of the sequence of alkylation and hydrogenation in Lensky would also have been prima facie obvious because such derivatization steps are independent for different functional groups. In addition, according to the Examiner, the limitations in the dependent claims are alternative operating parameters suggested in Devries.

The discussion above regarding the third and fourth obviousness rejections fully applies to this rejection. Lensky discloses hydrogenation of 1-benzyl-4-(5,6-dimethoxyindan-1-on-2-ylidene)-methyl-pyridinium bromide using platinum dioxide. Sugimoto I and Sugimoto II teach hydrogenation of 1-benzyl-4[5,6-dimethoxy-1-indanon)-2-ylidenyl]-methylpiperidine using palladium carbon. Devries discloses a scheme for the preparation of donepezil, but the starting material is 4-(5,6-dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester, not 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one. As such, no hydrogenation is disclosed. Again, none of the cited references teaches or suggests hydrogenation of 5,6-dimethoxy-2-(pyridin-4-yl) methylene indan-1-one (compound of formula (IV)), let alone with palladium metal on a support carrier (e.g., palladium carbon). As such, the combination of Vidyadhar, Sugimoto I, Sugimoto II and Devries fails to provide each and every limitation of claims 1-33 as is required for a finding of obviousness, rendering the rejection legally improper.

CONCLUSION

Appellants submit that claims 1-33 have been demonstrated to be patentable over the documents that were applied in the rejections. Accordingly, reversal of all of the rejections is appropriate and is respectfully solicited.

Respectfully submitted,

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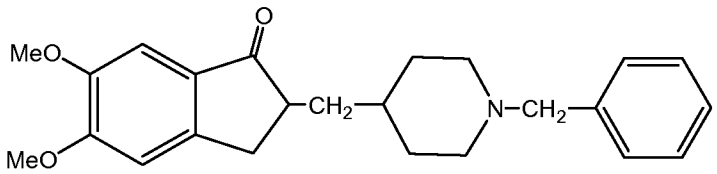
CLAIMS APPENDIX

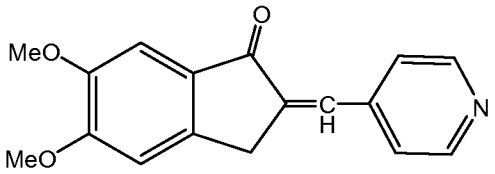
1. A process for preparation of donepezil which has the formula (I),



(I)

said process comprising:

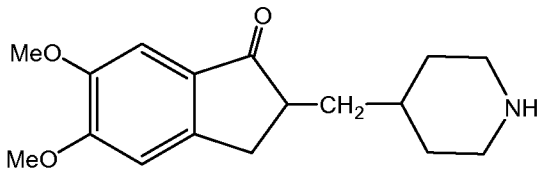
a) suspending a compound of the formula (IV):



(IV)

and a catalyst, which is palladium metal on a support carrier, in an alcoholic solvent;

b) hydrogenating the suspension at the hydrogen pressure of from about 1 to about 5 atmospheres and a temperature of from about 40 to about 90° C. until the hydrogenation reaction is substantially complete to obtain a compound of the formula (VI):



(VI) ;

c) isolating said compound of formula (VI); and

d) converting said compound of the formula (VI) to said compound of the formula (I).

2. The process of claim 1, wherein said step of isolating said compound of the formula (VI) includes

c.1) removing the palladium catalyst;

c.2) removing the alcoholic solvent to obtain a residue;

c.3) contacting said residue with water to obtain an aqueous solution of said residue;

c.4) adjusting the pH of said aqueous solution to a range of from about 9 to about 14;

c.5) contacting said aqueous solution having said adjusted pH with an organic extractant;

c.6) separating said organic layer containing said residue; and

c.7) distilling said extractant from said organic layer thereby obtaining a second residue of the compound of the formula (VI).

3. The process of claim 2, further comprising triturating the second residue in a non-polar organic solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, cycloheptane, diethyl ether, diisopropyl ether, diisobutyl ether, methyl tertiary butyl ether, and petroleum ether.

4. The process of claim 1, wherein said alcoholic solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol and tertiary butanol.

5. The process of claim 1, further comprising hydrogenating in the presence of acetic acid.

6. The process of claim 5, wherein said alcoholic solvent is methanol.

7. The process of claim 1, wherein said hydrogenation temperature is from about 60 to about 65 °C.

8. The process of claim 2, wherein said extractant is selected from the group consisting of dichloromethane, dichloroethane, chloroform and carbon tetrachloride.

9. The process of claim 2, wherein said pH is adjusted with a aqueous solution of a base selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate.

10. The process of claim 1, wherein said step of converting the compound of the formula (IV) to the compound of the formula (I) includes reacting the compound of the formula (VI) with benzyl bromide in a second alcoholic solvent in the presence of a second base at a temperature of from about 30 to about 80 °C.

11. The process of claim 10, wherein said second alcoholic solvent is selected from the group consisting of methanol, ethanol isopropanol, butanol acetone, ethylmethyl ketone, and 2-butanone.

12. The process of claim 10, wherein said second base is selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate and potassium bicarbonate.

13. The process of claim 10, wherein said second base is selected from the group consisting of triethyl amine, tributyl amine, tertiary butyl amine and pyridine.

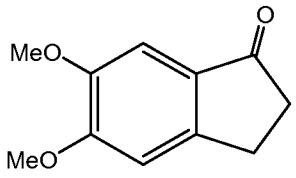
14. The process of claim 10, further comprising cooling the reaction mass to ambient temperature, filtering the reaction mass, diluting the filtrate with water and contacting the aqueous mixture with a second organic extractant.

15. The process of claim 14, wherein said second organic extractant is selected from the group consisting of isopropyl ether, methyl tertiary butyl ether, diethyl ether, toluene, benzene, ethyl benzene, xylene, hexane, cyclohexane and petroleum ether.

16. The process of claim 15, further comprising separating the organic layer and removing said second organic extractant therefrom to obtain a third residue.

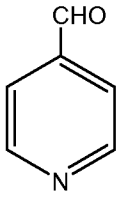
17. The process of claim 16, further comprising triturating said third residue in a non-polar organic solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, cycloheptane, diethyl ether, diisopropyl ether, diisobutyl ether, methyl tertiary butyl ether, and petroleum ether.

18. The process of claim 1, further comprising reacting a compound of the formula (II)



(II)

with a compound of the formula (III)

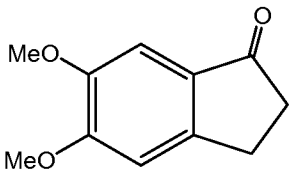


(III)

to obtain said compound of the formula (IV).

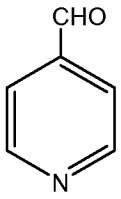
19. A process for preparation of donepezil, said process comprising:

a. refluxing a mixture of 5,6-dimethoxy indanone of the formula (II)



(II)

and pyridine-4-carboxaldehyde of the formula (III)



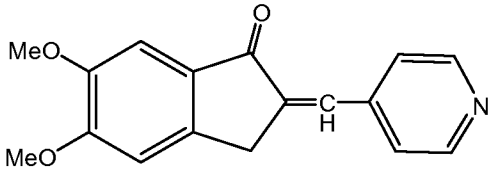
(III)

in toluene in the presence of p-toluene sulfonic acid until the reaction is substantially complete thereby a solid is formed;

b. cooling the reaction mixture to ambient temperature and filtering the solid;

c. suspending the filtered solid in an aqueous basic solution and stirring the suspension;

d. filtering the solid obtained in step c. to afford 5,6 dimethoxy-2(pyridin-4-yl)-methylene indan-1-one of the formula (IV):



(IV) ;

e. suspending the compound of the formula (IV) and palladium on carbon in an alcoholic solvent selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol and tertiary butanol in the presence of acetic acid in a hydrogenation vessel;

f. heating the reaction mixture of step e. under 1-5 atmospheres hydrogen pressure at a temperature of 40 to 90° C. until the reaction substantially completes;

g. cooling of the reaction mass of step f. to ambient temperature followed by filtering the catalyst;

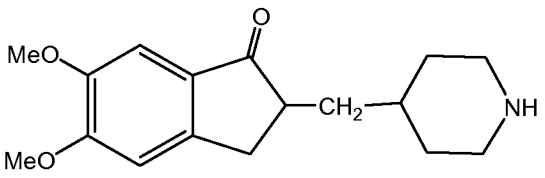
h. distilling the solvent from the filtrate obtained in step g. to get a residue;

i. dissolving the residue obtained in step h. in water and followed by washing with a chloro solvent selected from the group consisting of dichloromethane, dichloroethane, chloroform and carbon tetrachloride, and separating the aqueous layer;

j. adjusting the pH of the aqueous layer of step i. to 9 to 14 with a base solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate;

k. extracting the compound from the basified aqueous layer of step j. with an organic solvent selected from the group consisting of dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether and petroleum ether;

l. distilling the solvent from the reaction solution of step k., followed by triturating the residue in a non-polar organic solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, cyclo heptane, di ethyl ether, di isopropyl ether, di isobutyl ether and methyl tertiary butylether and petroleum ether, to afford 5,6-dimethoxy-2-piperidin-4-yl methyl-indan-1-one of the formula (VI):



(VI) ;

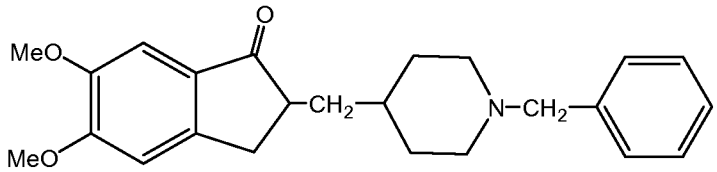
m. reacting the compound of the formula (VI) with benzyl bromide in a solvent selected from the group consisting of methanol, ethanol isopropanol, butanol acetone,

ethylmethyl ketone, and 2-butanone in the presence of a base selected from the group consisting of sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethyl amine, tributyl amine, tertiary butyl amine and pyridine at a temperature of 30-80°C., until the reaction substantially completes;

n. cooling the reaction mass to ambient temperature and followed by filtering the mass;

o. diluting the filtrate obtained in step n. with water and further extracting the compound into ether solvents selected from the group consisting of isopropyl ether, methy tertiary butylether, diethyl ether, toluene, benzene, ethyl benzene, xylene, hexane, cyclohexane and petroleum ether; and

p. distilling the solvent from the reaction solution of step o. followed by triturating the residue in a non-polar organic solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, cyclo heptane, di ethyl ether, di isopropyl ether, di isobutyl ether, methyl tertiary butylether and petroleum ether, to obtain the donepezil of the formula (I):



(I)

20. The process of claim 19, wherein said aqueous basic solution of step c. is a solution of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate.

21. The process of claim 19, wherein said aqueous basic solution of step c. is 10% w/v sodium bicarbonate solution.

22. The process of claim 19, wherein the catalyst for catalytic hydrogenation of step e. is 5% or 10% palladium over carbon.

23. The process of claim 19, wherein the catalyst for catalytic hydrogenation of step e. is carried out in the presence of 1 to 5 mole ratio of acetic acid with respect to the compound of the formula (IV).

24. The process of claim 23, wherein said mole ratio is 1.0 to 1.5.

25. The process of claim 1, wherein said carrier is carbon.

26. The process of claim 19, wherein the chloro solvent of step i. is dichloromethane.

27. The process of claim 19, wherein the aqueous base solution of step j. is 10% w/v potassium hydroxide solution.

28. The process of claim 19, wherein the non-polar solvent for trituration of step l. is petroleum ether.

29. The process of claim 19, wherein said alcoholic solvent of step (m) is ethanol.

30. The process of claim 19, wherein the inorganic base of step m. is sodium carbonate.

31. The process of claim 19, wherein the reaction temperature of step m. is 55-60°C.

32. The process of claim 19, wherein the aromatic hydrocarbon solvent of step o. is toluene.

33. The process of claim 19, wherein the non-polar solvent for trituration of step p. is petroleum ether.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.